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mTOR Signaling Fades POMC Neurons during Aging

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Hypothalamic POMC neurons contribute to the regulation of energy homeostasis and glucose metabolism. In this issue of *Neuron*, Yang et al. (2012) show that the mTOR pathway has a pivotal role in deterioration of POMC neurons during age-dependent obesity.

Obesity is a risk factor in age-related metabolic diseases including type 2 diabetes, cancer, and cardiovascular and neurodegenerative diseases. However, mechanisms explaining age-dependent changes in the central regulation of metabolism that result in obesity are not understood. It has been suggested that hypothalamic pro-opiomelanocortin (POMC) neurons, which are critical regulators of energy homeostasis and glucose metabolism, may play important roles in the etiology of chronological age-associated metabolic and neurodegenerative disorders (Xu et al., 2005; Halabe Bucay, 2008). Mammalian target of rapamycin (mTOR) is the target of rapamycin and a serine/threonine protein kinase that regulates cell growth, proliferation, and motility. Over the last decade, many laboratories focused on mTOR signaling to better understand the aging process and to develop antiaging strategies. Hypothalamic mTOR signaling was also found to be relevant for feeding behavior and peripheral metabolism through mediating signaling of nutrients and hormones (Cota et al., 2006; Mori et al., 2009). In this issue of *Neuron*, Yang et al. (2012) provide evidence that increased mTOR signaling in POMC neurons of the hypothalamic arcuate nucleus plays a crucial role in the development of age-dependent obesity.

POMC neurons, together with another population of arcuate nucleus neurons that coproduce neuropeptide Y (NPY), agouti-related protein (AgRP), and GABA, control food intake, energy expenditure, and glucose homeostasis. They project to various brain sites, such as the paraventricular hypothalamic nucleus, where they regulate melanocortin-4 receptor (MC4R) function. When elevated leptin and glucose levels trigger POMC neurons to fire, they secrete melanocyte-stimulating hormone (α-MSH). Food intake decreases, energy expenditure increases, and peripheral glucose metabolism is enhanced. When glucose and leptin levels decline during fasting or times of low food availability, NPY/AgRP neurons become active and POMC neurons become silent. Consequently, appetite increases, energy expenditure subsides, and lipid metabolism is favored over glucose utilization. α-MSH released from POMC cells is an agonist of the MC4R, while AgRP is an inverse agonist of MC4R. Activation and inactivation of MC4R in the paraventricular hypothalamic nucleus is an important regulator of feeding.

Yang et al. (2012) demonstrate that POMC neurons deteriorate in aged mice that display obesity (Figure 1). POMC neurons have diminished neuronal firing and α-MSH secretion. In order to clarify whether POMC neuronal silencing in these animals can be influenced by synaptic inputs, they evaluated the resting potential and action potential firing of POMC neurons after blockade of glutamate and GABA receptors. They identified that when an ATP-sensitive potassium (K_{ATP}) channel blocker was present, depolarization of POMC neurons in aged mice was restored, suggesting that age-dependent deterioration of POMC neuron firing is associated with K_{ATP} channel activation.

One of the striking findings of Yang et al. (2012) is that mTOR activity was elevated in POMC neurons of the aged mice, leading to cell hypertrophy. Since increased mTOR signaling gives rise to hypertrophy of neuronal cells (Meikle et al., 2008), their observation suggests that cell hypertrophy and obesity-related deterioration of POMC neurons might be causally related. The work of Yang et al. (2012) built on a previous report describing a role for mTOR signaling in the control of POMC neurons (Mori et al., 2009). Mori et al. (2009) evaluated the effects of deleting the *Tsc1* gene, which is a major upstream inhibitor of mTOR. They demonstrated that elevation of mTOR signaling in POMC neurons resulted in enlarged POMC neuron somas and reduced neurite projections to the PVN (Mori et al., 2009). Plum et al. (2006) also reported that inactivation of POMC neurons by POMC-specific deletion of PTEN, a lipid phosphatase that inactivates K_{ATP} channel by decreasing PIP_3 content, resulted in hypertrophy of POMC cells (Plum et al., 2006). In the current paper, Yang et al. (2012) extend these findings to implicate mTOR in age-induced deterioration of POMC neurons leading to hyperphagic obesity. Nevertheless, it remains unclear how hypertrophy of POMC neurons leads to dysregulation of neuronal projections and neurotransmitter release and what the intracellular and extracellular triggers of this process are. An intriguing recent finding was the observation of peroxisome proliferation in POMC neurons associated with diet-induced obesity (Diano et al., 2011). This process is related to glucose and lipid overload to POMC neurons (Diano et al., 2011), which is also a fundamental prerequisite of cellular growth. In that case, reversal of peroxisome proliferation resulted in restoration of POMC neuronal firing by enhancing generation of reactive oxygen species (Diano et al., 2011). Thus, it is possible that mTOR-related cellular growth of POMC neurons may also impair cellular metabolism and ROS control.

Yang et al. (2012) explored whether constant elevation of mTOR signaling in either POMC neurons or NPY/AgRP neurons may lead to obesity or weight loss using an elegantly designed mouse model. To accomplish cell-selective upregulation of mTOR signaling in either of these cell populations, they crossed POMC-Cre or AgRP-Cre mice with floxed TSC1 mice. TSC1 is a negative regulator of mTOR; hence, its cell-specific knockdown in either POMC or AgRP neurons would lead to chronically elevated mTOR signaling in these cells. They confirmed the findings of Mori et al. (2009), showing that elevation of mTOR signaling induced by deletion of the *Tsc1* gene in POMC neurons silenced POMC neuron activity and resulted in hyperphagic obesity even in young mice. Intriguingly, however, deletion of the *Tsc1* gene in NPY/AgRP neurons had no effect on the firing rate and soma size of these neurons. They further corroborated these findings by investigating the effect of intracerebral infusion of rapamycin, an inhibitor of mTOR signaling, on metabolic phenotype and neuronal activity. Rapamycin has been proposed as a putative promoter of longevity and suppressor of metabolic disorders and neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. Central administration of rapamycin rescued silencing and hypertrophy of POMC neurons during chronological aging and suppressed age-dependent obesity. On the other hand, consistent with patterns of the conditional KO mice deleting *Tsc1* gene in NPY/AgRP neurons, rapamycin had no effect on NPY/AgRP neuronal activity. One possible explanation for the "insensitivity" of NPY/AgRP neurons to rapamycin is that NPY/AgRP neurons may be more reliant on other intracellular pathways for their firing, such as fatty acid metabolism (Andrews et al., 2008).

To elucidate an underlying mechanism for the observed phenomenon, Yang et al. (2012) revealed a contribution of K_{ATP} channel activity in the age-related silencing of POMC neurons. Elimination of the *Tsc1* gene in POMC neurons of young mice gave rise to the elevation of K_{ATP} channel activity. Increased K_{ATP} channel activity leads to potassium outflow from the neurons, resulting in hyperpolarization of membrane potential. This effect, in turn, can lead to silencing of POMC neurons and consequent diminished α-MSH release even in the presence of elevated leptin levels. Because α-MSH is the critical activator of MC4 receptors that promote satiety, impaired release of this peptide, by default, will promote feeding.

Glucose intolerance and insulin resistance are common symptoms of type 2 diabetes and are closely linked to body mass index (BMI). Yang et al. (2012) observed a discrepancy in the relationship between BMI and glucose intolerance in POMC-specific *Tsc1* KO mice. They argue that specific activation of K_{ATP} channels in POMC neurons may improve glucose metabolism, because a previous study described that hypothalamic activation of K_{ATP} channels can, under very specific circumstances, lead to enhanced glucose metabolism (Pocai et al., 2005). However, studies have shown that there is positive interaction between POMC neuron activity and glucose metabolism regardless of feeding behavior and adiposity (Berglund et al., 2012). Thus, more studies are needed to reconcile these differential effects. Whether the observations of Yang et al. (2012) could lead to the development of successful strategies to interfere with age-associated metabolic impairments will be answered in the future.

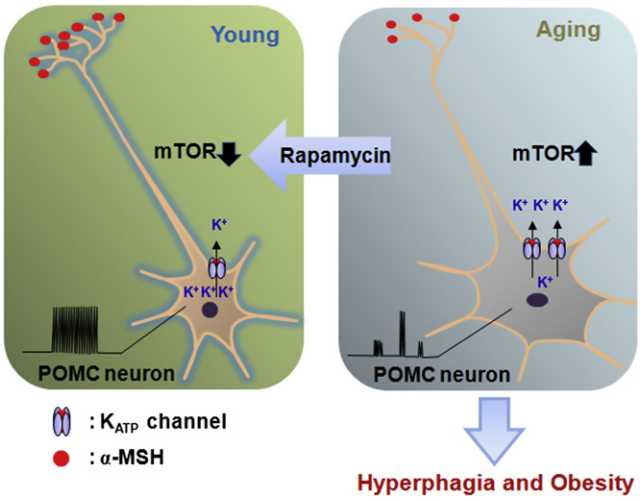

Figure 1. Contribution of mTOR to Age-Induced Deterioration of POMC Neurons

Activation of mTOR signaling in aging mice leads to hyperphagic obesity by triggering deterioration of POMC neurons. Neuronal somas become hypertrophic, neurite projections to the PVN are impaired, and neuronal activity and leptin-induced secretion of α-MSH is diminished. K_{ATP} channels play a crucial role in age-induced silencing of POMC neurons by controlling membrane potential of these cells. Rapamycin, a blocker of mTOR, restores cell size and activity of POMC cells.

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